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REVIEW

Evaluation of the child with atopic dermatitis

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Summary

Atopic dermatis (AD) is a very common inflammatory skin disease in childhood. Various doctors such as paediatricians, general practitioners, allergologists and dermatologists are regularly consulted by these children and their parents, but there is no clear consensus on the diagnostic work-up that should be performed when evaluating a child with eczema. A careful history, clinical examination and adequate documentation of disease severity are essential in all children with eczema, irrespective of their disease severity. AD is a clinical diagnosis; diagnostic criteria, such as the UK diagnostic criteria, can be helpful for an accurate definition of the disease. A careful history, including alarm symptoms, respiratory symptoms and the impact of the disease on psychosocial functioning is important. Clinical scoring lists such as SCORAD and EASI are well validated for clinical studies; they are, however, not very suitable tools in clinical practice. More simple scoring systems, such as Three Item Severity Score (TIS) and Investigator Global Assessment (IGA), are more easy to use for clinical record keeping in daily practice. Allergen testing in children with AD without a history of acute non-eczematous reactions after allergen exposure is not necessary. In very young children with eczema, not yet exposed to foods, routine allergen testing is not necessary. If in individual cases, the decision is made to perform allergen tests, oral challenges should performed to confirm the diagnoses of food allergy.

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Introduction

Atopic dermatitis (AD) is a very common inflammatory skin disease in childhood and has a large impact on the quality of life (QOL) of children and their families. In developed countries, AD is affecting 15–20% of the children [1, 2]. In a recent population-based prospective birth cohort study in Denmark (n = 562 children) [3], the cumulative incidence of AD, based on the criteria of Hanifin and Rajka at the age of 6, was 22.8%.

AD usually starts within the first 6 months of life. Remission during life occurs before the age of 15 years in 60–70% of cases, although some will relapse later. There is a large variability in the severity of the disease: most children have mild disease (70–84%) [4–6] and are treated by general practitioners. Young age at onset (first year of life), coexistent respiratory allergy and urban living predicted more severe disease [7]. In a German birth cohort study on the natural course of AD from birth to age of 7, the strongest risk factor for persistent AD was the severity of the disease at early age [8].

Genetic factors are thought to be involved in the development of AD. In European adults, null mutations in the epidermal barrier protein filaggrin (FLG) gene resident on the epidermal differentiation complex (1q21) were a predisposing factor for persistent eczema of early onset and AD with elevated IgE levels [9, 10]. In a systemic review and meta-analysis on FLG defects and risk of developing allergic disorders, van den Oord et al. found strong evidence of the relation between fillagrin mutations and AD in people manifesting increased severity and persistence of disease [11].

Most of the children have a family history of atopic diseases, and a high percentage of the children with AD are sensitized to food- and/or aero-allergens. In a recent study in 2184 children with AD (mean age 17, 6 months) who participated in a multicenter study, de Benedictis et al. found sensitization to at least one allergen (aeroallergen and/or food allergen) in 55.5% of

the children [12]. Despite the high percentage of sensitisation, the percentage with clinical relevant allergy is much lower [13]. Children with AD are at risk for developing asthma and rhinitis [14], and the risk of development of asthma possibly correlates to the severity of AD [15].

In most cases, AD can be easily established by clinical criteria. However, there is no clear consensus on the diagnostic work-up that should be performed when evaluating a child with eczema.

In this review, several aspects of the diagnostic work-up in children with AD, such as diagnostic criteria, clinical scoring and relevance of allergen testing, is discussed .

Diagnosis

Atopic dermatitis is a clinical diagnosis. As AD represents a wide spectrum of dermatological manifestations, several sets of diagnostic criteria have been developed in an attempt to better define the disease.

The most frequently used criteria are those of Hanifin and Rajka, presented in 1980 [16]. These criteria consist of four major and twenty-three minor criteria, and are based on consensus between experienced dermatologists. Only two validation studies were published in 1994 and 2006; however, both were hospital-based. The criteria of Hanifin and Rajka are not really manageable in daily practice, because their use is time consuming.

A questionnaire was developed in 1991 for the International Study of Asthma and Allergies in Childhood (ISAAC) to facilitate international research collaboration in AD and other allergic diseases. This questionnaire is primarily used to assess prevalence, and there are no data on specificity and sensitivity [17].

In 1997, the UK diagnostic criteria for AD were introduced by Williams et al. [18] (Table 1). The UK diagnostic criteria are a refinement of criteria of Hanifin and Rajka, and consist of one mandatory and five major criteria. The criteria were designed for clinical and epidemiological studies, but they are easy to perform and may be acceptable in daily practice. A slight modification is needed when children are assessed. The UK diagnostic criteria were frequently validated in both hospital and population-based settings, and the criteria were also tested for repeatability.

Table 1. UK diagnostic criteria

UK diagnostic criteria
child must have itchy skin conditions in the past 12 months
PLUS three or more of:
History of involvement of skin creases
Personal history of asthma or hayfever*
History of generally dry skin in the past year
Visible flexural dermatitis#
Onset below age 2**

*history of atopic disease in 1st degree relative if age < 4 years.
#as defined by photographic protocol.
**not used in children < 4 years.

In 1998 Bos et al. proposed the millennium criteria [19], in which the presence of allergen-specific IgE is mandatory for the diagnosis AD. The presence or absence of atopy, however, does not help our clinical ability to diagnose eczema, and in some countries, there is no association of flexural eczema with IgE or sensitization [20]. Validation studies of the millennium criteria are, however, lacking so far.

In a systemic review, Bennickmeijer et al. summarized the evidence concerning the validity of diagnostic criteria for AD [21]. The conclusion of this systemic review was that from all criteria for the diagnosis AD, the UK diagnostic criteria are the most extensively validated.

The UK diagnostic criteria are easy to perform and manageable in daily practice.

Differential diagnosis

In early childhood, AD can be easily confused with seborrhoic dermatitis (SD). Pruritus, localization of the lesions on forearm and shins, elevated specific serum IgE and a family history of atopy in AD are mostly seen in AD. SD often begins before the age of 6 weeks, and the skin lesions are mostly located in the axillae and napkin area; AD often spares the napkin area. SD can also precede AD.

Scabies might be difficult to differentiate if it presents with an eczematous reaction. In scabies, the lesion presents with more acute onset and are localized more in the axillae, groins and genital area, with sparing of the face in contrast to AD. Vesiculation on the palms and soles in infants is common in scabies. Often more family members are affected at the same.

Although psoriasis is rare in infancy, it might present with pruritus and demarcated plaques without silver scales on the cheeks. In older children, dermatomycosis might look like AD, but presents without pruritus. Clinically relevant allergic contact dermatitis is rare in infancy, but an irritant contact dermatitis might occur.

In very recalcitrant cases, other more rare diseases should be suspected; for instance, genodermatoses such as Netherton syndrome, immunodeficiencies such as Wiskott-Aldrich syndrome, metabolic disturbances such as phenylketonuria or nutritional zinc deficiency (acrodermatitis enteropathica) and malignancies such as Langerhans cell histiocytosis or cutaneous T cell lymphoma. [Online Mendelian Inheritance in Man (OMIM); http://www.ncbi.nlm.nih.gov/omim; AD MIM ID # 603165, 605803].

Co-morbidity in children with AD: asthma and rhinitis

Children with AD have an increased risk of developing other atopic diseases such as food allergy, asthma and allergic rhinitis (AR). These diseases can develop in a sequential way, in early childhood AD and/or food allergy, later on asthma and/or rhinitis. This phenomenon is called 'the allergic march', and has been supported by several studies, mainly cross-sectional. In a systematic review evaluating 13 prospective cohort studies, of which four were birth cohort and nine were eczema cohorts, van der Hulst et al. showed an increased risk of developing asthma in children with eczema (odds ratio 2.14) [14]. Spergel [22] suggested that the development of asthma might be related to a subgroup of patients with severe eczema and specific IgE to aeroallergens. Allergen sensitization may be a risk factor for developing airway disease in children with AD. Lowe et al. found that children with AD and allergen sensitization had a substantially greater risk of asthma (odds ratio 3.52) and AR (odds ratio 2.91) than children with eczema without allergen sensitization [23]. In the earlier mentioned German birth cohort study [8], the relationship between AD and childhood asthma was also analysed. Early AD was associated with asthma at school age, but in many of these asthmatic children, wheezing manifests before or with the onset of AD. Early wheeze and a specific sensitization pattern (sensitization to wheat, cat, mite, soy or birch) were significant predictors for wheezing at school age, irrespective of AD. AD without these cofactors constituted no risk of subsequent wheeze.

More recently, genetic studies on the relationship between AD and asthma have been performed. Two losses of function polymorphisms (FLG R501X- and 2282del4) in the FLG gene encoding for an epidermal barrier protein have been reported to be predisposing factors for AD and concomitant asthma [24]. So, there seems to be a relation between AD and children's asthma, but not with adult onset-asthma [25]. It is important to realize that in early childhood, viral induced wheezing is very prevalent, and that not all wheezing is asthma.

Severity scoring in children with AD

Assessment of disease activity in AD is routinely performed in clinical studies, but is not regularly used in clinical practice. However, the use of valid and reliable clinical outcome measures may improve good evidence-based clinical practice. Clinical scoring by trained physicians using properly validated scoring lists is a good tool for registration of disease severity and follow-up of therapy. However, clinical scoring remains rather subjective and requires training; therefore, many attempts have been made to search for objective serum parameters that correlate with disease activity.

Clinical scoring

Clinical scoring is a non-invasive method to assess the disease activity in children with AD. Clinical scoring requires thorough inspection of the whole skin, and it is a very useful tool for evaluation of therapy.

A large number of clinical scoring lists for AD have been developed for both children and adults; however, most of them are not properly validated. In a systematic review, Schmitt et al. assessed the validity, reliability, sensitivity to change and practical use of outcome measures for disease activity in AD [26]. The authors concluded that of the 20 outcome measures that were studied, only EASI (Eczema Area and Severity Index), POEM (Patient-oriented Eczema Measure) and SCORAD (Severity Scoring of Atopic Dermatitis index) have been validated adequately enough at present to recommend their use in clinical trials and every day practice. EASI and SCORAD are based on the assessment of a physician, and are therefore sometimes referred as 'objective', whereas POEM is scored by the patient or caregiver. SCORAD and EASI report both extent and the intensity of the disease.

The SCORAD uses six intensity parameters (erythema, oedema/population, oozing/crust, excoriation, lichenification and dryness) on one representative lesion; the EASI uses four intensity parameters (redness, thickness, scratching and lichenification) on four body area (head/neck, upper limbs, trunk, lower limbs). The EASI is frequently used to assess severity of eczema in children with AD. Although EASI is easier to perform than SCORAD, it still requires training. To provide caregivers of children with AD a tool to report the severity of their child's skin disease, the Self-Administered EASI (SA-EASI) was developed. A significant correlation was found between the SA-EASI and both EASI and SCORAD [27, 28].

Although both SCORAD and EASI are well validated for clinical studies, they are not very useful tools in clinical practice. A more simple scoring system for eczema severity, such as the Three Item Severity score (TIS), is far more easy to use in daily practise. This score is based on the evaluation of erythema, oedema/papulation and excoriation on a scale from 0 to 3, and correlates well with the SCORAD (Rank Spearman r(s) = 0.86)[29]. The disadvantage of the TIS score is that it does not take into account the body surface area (BSA), which is a very important factor for determination of disease severity. A combination of a simple severity scoring system in combination BSA, which does not exist at the moment, should be most appropriate in daily practice.

Another useful tool in the follow-up of the patient is the Investigator Global Assessment (IGA), which is a static evaluation (no reference to baseline) of the overall severity of AD at a given time. The IGA correlates very well with the EASI in the follow-up of the patient, and is easy to perform in daily practice [30].

Development of scoring lists for clinical record keeping is one of the main issues of the HOME (Harmonising Outcome Measures for Eczema) working group [31].

Serum parameters

In 20 adult patients with AD, Gutgesell et al. compared serum levels of soluble E-selectin, s-VCAM (soluble vascular cell adhesion molecule-1) and ECP (eosinophil cationic protein) with SCORAD values, every 4 months for 1 year . Only sE-selectin showed statistically significant correlation with the SCORAD score [32].

In a large population of patients with allergic diseases (n = 445), Hijnen et al. found that serum level of thymus and activation-regulated chemokine (TARC) was specifically elevated in patients with AD, irrespective of coexistence of respiratory allergy. Serum TARC level significantly correlated with disease activity [33].

In a more recent study, the serum TARC level was assessed in children with AD. After treatment with topical corticosteroids, the magnitude of the decrease in SCORAD index correlated significantly with the decrease in serum TARC level [34]. Serum TARC level seems to be a good objective marker for disease activity in children with AD, when taking into account the different normal ranges in different age groups.

Is allergy testing with aeroallergens recommended in the diagnostic work-up of the child with AD?

Allergen exposure

Although a large number of children with AD are sensitized to one or more aeroallergens [12], the clinical relevance of allergen exposure in AD remains uncertain. The sensitization pattern changes throughout childhood; in a German cohort study [35], the prevalence of sensitization to each allergen increased steadily throughout childhood, and a hierarchy of sensitization prevalence (grass > birch > mites > cat > dog) was maintained from 5 years of age onwards.

Until now, there is no clear evidence that allergen exposure early in life is associated with an increased risk of eczema. In a birth cohort study of 593 children followed until the age of 8, Harris et al. found [36] no association between early exposure to house dust mite (HDM)- or cat allergen and the occurrence of AD. In addition, reduction of allergen exposure in early life using mite impermeable mattress covers had no effect on sensitization and prevalence of AD in high-risk children (atopic mother), recruited prenatally [37] .

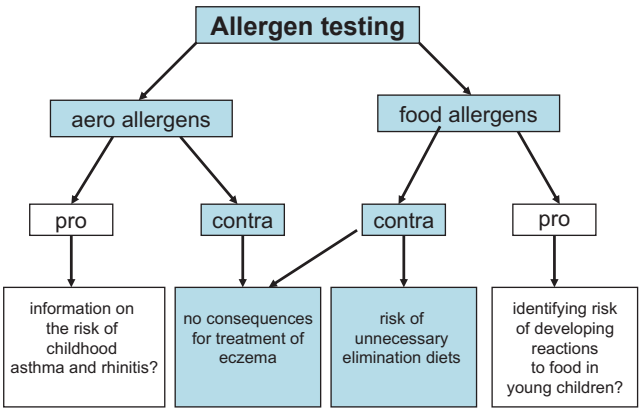

Fig. 1. Pro's and contra's of allergen testing in children with AD.

Effects of allergen exposure on established eczema are difficult to study. The patients' history is often unreliable, because of the chronic relapsing course of AD. In a large multicenter observational study in both children and adults with AD, 10–39% of patients reported worsening of eczema after aeroallergen contact (mostly HDM)[38]. In a study in children with AD, Kramer et al. described two patterns of eczema: a summer-type patterns with aggravation of symptoms in summer and a winter-type pattern where symptoms mainly occurred during the winter [39]. Children with a summer-type pattern (18/39 children) experienced more symptoms (itch 16% higher, extend 19% higher) during days with high grass-pollen exposure.

In an experimental setting, eczematous reactions can be provoked by applying aeroallergens on the skin in both adults and children with AD [38, 40–42]. In this model, called the Atopy Patch Test (APT), aeroallergens are applied to the skin for 48–72 h. Eczematous reactions are observed in 30–50% of sensitized adult AD patients, and in children with AD higher percentages [42]. Although the APT with aeroallergens is a good research tool, its role in the diagnostic work-up in AD is not yet established. Apart from problems with standardization of the test, there is no gold standard to compare with [43].

Allergen avoidance

Both positive and negative results of HDM avoidance measures on severity of eczema have been described in children and adults with AD. The studies are difficult to compare because of differences in avoidance methods used, and differences in study duration. In a 6-months study, Tan et al. found a decrease in severity of eczema

in both the active and placebo group in adults and children with AD (mean age 10 years): a significant greater improvement was observed in the active group [44]. The use of HDM-impermeable encasings in children and adults with AD (age 8–50 years) during 1 year resulted in a significant decrease in Der p1 and Der f1 allergen concentrations in the active group, but no significant changes in clinical parameters between the groups were found [45]. These latter results are in accordance with the results of Gutgesell et al. [46]. Extensive HDM avoidance measures in 41 young children with AD (mean age 3.9 years) resulted in a significant improvement of SCORAD value after 12 months; a major limitation of this study is that a placebo-controlled design was only used in a short period of 2 months [47].

In conclusion, although a large number of children with AD are sensitized to aeroallergens, there is no evidence that exposure to aero-allergens influences the prevalence of AD. There is only limited evidence that aeroallergen exposure aggravates already existing eczema. Giving the conflicting outcome of the studies, allergen avoidance measures cannot be recommended to relieve symptoms. Therefore, aeroallergen testing in the diagnostic work-up of the child with eczema does not seem to have clinical consequences. The only reason to perform aeroallergen testing might be the identification of those children with AD, who may be at risk for developing airway disease (see section 3). As was mentioned earlier, the development of asthma might be related to a subgroup of patients with severe eczema and specific IgE to aeroallergens [22], whereas the existence of AD alone constituted no risk of subsequent wheeze [8]. Aeroallergen testing is also indicated in children with AD and actual/typical airway symptoms (Fig. 1).

Is allergy testing with food allergens recommended in the diagnostic work-up of the child with AD?

Sensitization to food allergens is very common in children with AD. In a total of 2184 children with AD (mean age 17.6 months) recruited from 94 centres in 12 countries, sensitization to any food allergen was reported in nearly 50% of the children. For egg white, cow milk and peanut, the percentages were, respectively, 41.9%, 27.4% and 24.4% [12].

However, sensitisation does not necessarily indicate clinical allergy. A recent retrospective study on the outcome of oral food challenges in children with AD using elimination diets mostly based on sensitisation demonstrated that, depending on the reason for avoidance, 84–93% of the avoided foods could be returned to the diets. These data indicate that the vast majority of foods that had been restricted could be tolerated [48].

In the literature, a wide range of percentages of food allergy in children with AD is reported, ranging from 20 to 80% [49, 50]. In 1998, Eigemann [51] described that approximately one-third of the children with refractory moderate to severe AD had an IgE-mediated allergy to food. However, not all children in this study underwent double-blind placebo-controlled (DBPC) food challenges.

In a recent birth cohort study (n = 562 children, age 0–6 years), less than 15% of the children with AD had confirmed food allergy [52]. All children were examined for the development of AD using Hanifin-Rajka criteria and for food allergy using interviews, skin prick test (SPT), specific IgE and food challenges, according to EAACI guidelines.

There is some indirect evidence that children with severe AD are at more risk for developing type I food allergy than children with mild AD. Studies in children with AD, recruited from tertiary centres, (university clinics) report higher percentages food allergy than birth cohort studies (more than 30% vs. less than 15%) [51, 52]. It is likely that most children treated in tertiary centres have more severe forms of AD. Furthermore, in a birth cohort study in 620 infants with a family history of atopic diseases, Hill et al. found that the relative risk of an infant with AD also having IgE-mediated food allergy was 5.9 for the most severe group [53]. In this study, the severity of eczema was quantified by dividing the children into four groups according to nurse-recorded topical steroid use; the adverse reactions to food were only documented by parental interview with a research nurse, and no food challenges were performed.

Until now, there are no hard data to support that children with severe AD will develop more severe reactions to food than children with milder forms of AD, and it is not possible to identify those children with AD who are at risk of developing immediate-type food allergy. However, recent data in 71 peanut allergic, food-challenge positive children suggest that FLG mutations represent a significant risk factor for IgE-mediated peanut allergy, suggesting a role for epithelial barrier dysfunction in the pathogenesis of food allergy in AD. This association was replicated in a larger Canadian study in 390 patients; however, in this study population, not all patients underwent food challenges [54]. These data need to be conformed in larger groups.

The level of specific IgE can be helpful to predict a clinical reactions to food in children with eczema [55, 56], but do not predict the severity of the reaction.

Effect of food allergy on eczema

As food allergy is relatively common in children with AD, food allergen testing is relevant for confirming the diagnosis of type I food allergy these children. However, the role of food allergens in worsening eczema is a matter of debate.

In the position paper of the EAACI concerning reactions to food in AD [50], three different reaction types are described. First, immediate-type non-eczematous reactions in which the clinical symptoms include skin symptoms such as urticarial rashes, and/or non- cutaneous symptoms such as gastrointestinal or respiratory symptoms or anaphylaxis. The second reaction type that is described includes isolated eczematous reactions, in which worsening of eczema occurs after hours to days. Eczematous reactions may also appear with preceding acute symptoms (reaction type 3: combined reactions).

Isolated eczematous reactions after food exposure in AD are very difficult to diagnose due to the unpredictable course of the eczema. The APT with food seemed to have a positive predictive value for isolated eczematous reactions; however, it is not recommended for routine diagnosis of food-induced eczema by the recent EAACI position paper. Eczematous reactions to food can only be properly diagnosed by oral food challenges (OFC) [50].

The recommended challenge protocol from the EAACI for the detection of eczematous reactions in AD includes a diagnostic elimination diet over a period of 4–6 weeks with the suspected food items. If topical steroids are necessary to control the eczema, this treatment should be continued through the entire phase of the oral food-challenge procedure. According to the position paper, food challenges should be ideally preformed in a placebo-controlled design. The kin must be scored by an established eczema score (e.g. SCORAD) before OFC and at least after 24 h; a difference of at least 10 SCORAD points is usually considered as a positive reaction.

Niggemann et al. [57] performed a retrospective analysis of the clinical outcome of 387 double-blind placebo-controlled food challenges (DBPCFC') in 107 children with AD. Clinical reactions including urticara, angio-oedema, wheezing, vomiting, diarrhoea abdominal pain or exacerbation of eczema from 2 h after challenge were found in 25% of the children. In this study, there is no clear definition of eczematous reactions after challenge.

In a more recent analysis of 106 DBPCFC's performed in 64 children with AD (median age of 2 years), Breuer et al. found only six isolated eczematous reactions (three after challenge with wheat, two after cow's milk and one after Henn's egg challenge [58]. A late eczematous reaction in this study was defined as an increase of > 10 SCORAD points > 6 h after challenge.

These data suggest that isolated eczematous reactions after food challenge do exist, although they are quite rare. Differences in number of reported isolated eczematous reactions after food challenge largely depend on the definition of the reaction.

Effects of food allergen avoidance on eczema

Many studies addressed the effect of food elimination diets on eczema severity in children with AD. Recently, a systematic review of randomized controlled trials to assess the effect of dietary exclusions for the treatment of eczema in adults and children was performed [59, 60]. Nine trials with 421 participants were included and divided in three main categories: egg and milk exclusion diets (six studies, $n = 288$), few foods diet (one study, $n = 85$) and elemental diet (two studies, $n = 48$). Primary outcome measures were changes in parent-rated or mother-rated symptoms, such as itching or sleep loss (short-term,< 6 weeks) and reduction in number of flares or reduced need for other treatments (long-term, > 6 months). Overall interpretation of the studies was difficult because of poor methodological quality, and most studies were performed in unselected patients with AD (not tested for food allergy). In addition, the long-term outcomes and consequences of an egg- and milk-free diet were not discussed in any of the studies. The conclusion of this systematic review was that there is no evidence of benefit in the use of an elemental or few-foods diet in unselected cases of AD. There also appears to be no benefit of egg- and milk-free diet in unselected patients with AD. There may be some benefit in using an egg-free diet in infants with suspected egg-allergy who have positive specific IgE to eggs. In a randomized controlled trial, Lever et al. [61] found that an egg-free diet in children with AD and egg allergy (specific IgE and DBCFC) resulted in a significant decrease in affected body surface area and eczema severity compared with normal diet. The elimination period, however, was only 4 weeks.

In conclusion, sensitization to food allergens is very common in children with AD; however, the majority of cases are not clinically relevant . Exposure to food can possibly result in an isolated eczematous reaction in a very small number of children. Until now, there is no strong evidence that elimination diets result in an improvement of eczema. Therefore, food allergen testing in the diagnostic work-up of children with eczema, without a history of non-eczematous reactions, does not seem to have clinical consequences, and can result in unnecessary elimination diets (Fig. 1).

Evaluation of psychosocial problems in children with AD and their parents

Chronic diseases like AD can have physical and psychological effects that affect social functioning. About 20% of the children with AD have moderate to severe AD [62, 63]. Their topical treatment is time consuming and takes at least 40 min every day. The QOL in chil-

dren with AD is worse than in children with asthma and diabetes and comparable with children with cystic fibrosis and renal diseases [64]. The impact on QOL is related to severity of AD [65]. Children with moderate to severe AD suffer from time-consuming topical treatment, itching, scratching and soreness, which cause sleeplessness in over 60% of the children [66]. Sleep deprivation leads to tiredness, mood changes and impaired psychosocial functioning of the child and family, particularly at school and work. Embarrassment, comments, teasing and bullying frequently cause social isolation and may lead to anxiety, depression or (school) avoidance behaviour and severe sleep disturbances. The child's life is often restricted, particularly with respect to clothing, holidays, staying with friends, owning pets, swimming or the ability to play or do sports. Restriction of normal family life, difficulties with complicated treatment regimes and increased work in caring for a child with eczema lead to parental exhaustion and feelings of hopelessness, guilt, anger and depression [67–71].

Besides the impact on QOL, most parents are worried about side-effects of using topical corticosteroids, such as skin thinning and systemic absorption, leading to effects on growth and development [72]. These worries can result in less compliance with topical corticosteroids and consequently less control of the disease.

QOL questionnaires, such as The Children's Dermatology Life Quality Index (CDLQI) [67], can be helpful in the evaluation of psychosocial problems and can additionally be used as a follow-up parameter during treatment.

Discussion

AD is a very common disease in childhood. Various doctors such as paediatricians, general practitioners, allergologists and dermatologists are regularly consulted by these children and their parents. In our opinion, it is not necessary to perform an extensive diagnostic work-up in every child with AD. When performing diagnostic tests, it is always important to realise what the clinical consequences of a specific test are and to discuss this thoroughly with the parents and the child. The evaluation of the child with eczema can be divided in patients' history, clinical examination and diagnostic work-up for allergy (Fig. 2).

History

A careful history, including alarm symptoms such as sleep disturbances, failure to thrive, recurrent/abnormal infections and chronic diarrhoea and/or vomiting should be performed in all children with AD to exclude systemic diseases. Also, the impact of the disease on psychosocial functioning of the child and family should be discussed. Special attention should be paid to anxiety related to the disease and treatment, sleeplessness, school performance, embarrassment and teasing.

A global exploration of respiratory comorbidity should be performed in every child with eczema. This implies a careful history of wheezing during the night and/or during exercise, coughing, nasal obstruction and/or nasal discharge, sneezing and eye symptoms (itch, running eyes). For more detailed and standardized information on respiratory allergy, for instance in clinical trials, the ISAAC questionnaires can be used for different age groups. (http://isaac.auckland.ac.nz). Early detection and adequate treatment of other allergic diseases can reduce comorbidity in the child with AD.

The most difficult part of the diagnostic work-up of the child with eczema is to investigate the effect of possible provocative factors. These factors are difficult to assess because eczema has a relapsing, remitting course with frequent and unexplained fluctuations in disease severity. In most cases, the history of child and parents can give important information on irritating factors on eczema, such as water and soap contact, sweating, smoke, stress, clothing and climate changes. History can also be helpful for identifying non-eczematous reactions after allergen exposure, such as urticar-

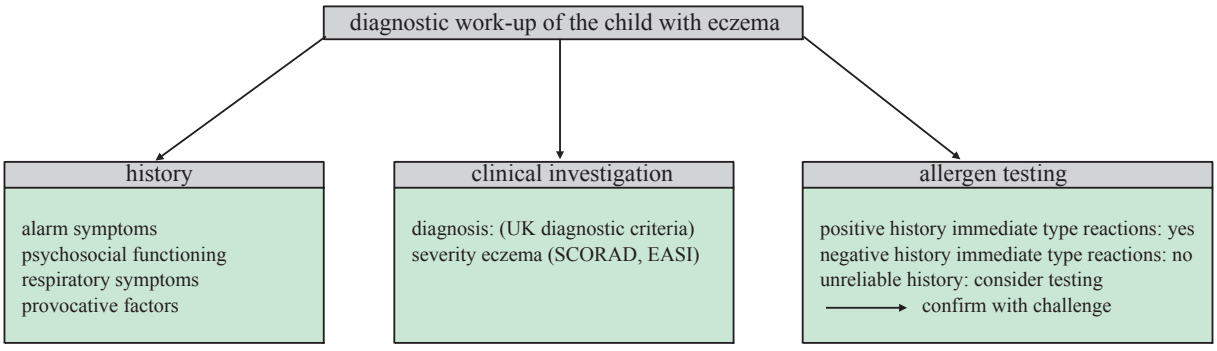

Fig. 2. Summary of the diagnostic work-up of the child with eczema.

ial rashes, and/or non- cutaneous symptoms, such as gastrointestinal or respiratory symptoms or anaphylaxis.

Clinical examination

An important part in the diagnostic work-up is the accurate diagnosis. Diagnostic criteria, such as the UK diagnostic criteria, may be helpful. When diagnosis remains doubtful or when the child is unresponsive to regular treatment, referral to a dermatologist is necessary to exclude more rare diseases mentioned in section 2 (differential diagnosis).

Adequate registration of disease severity is also an important part of the diagnostic work-up in a child with eczema, to ensure reliable evaluation of therapeutic interventions. A careful description of skin lesions, localization and severity of the disease requires training and takes time. Therefore, it is often more practical and time saving to use standardized clinical scoring lists. The best validated scoring lists are the SCORAD and the EASI score. The availability of digital scoring lists on the internet facilitates the use of these lists, for instance the SCORAD Calculator (http://adserver.sante.univ-nantes.fr/Compute.html). Using this programme, SCORAD values can be calculated within a few minutes. The Self-Administered EASI (SA-EASI) is a useful tool for children with AD and their caregivers to evaluate the severity of the eczema at home.

At this moment, the use of serum markers in the evaluation of disease severity should be limited to research purposes in specialized centres and to clinical trials. Further research on usefulness for daily practice is necessary.

Diagnostic work-up for allergy

As was mentioned earlier, history can be helpful for identifying immediate-type non-eczematous reactions after allergen exposure, and in those cases, allergen testing might help to identify the suspected allergen [73]. Isolated eczematous reactions > 2 h after allergen exposure are quite rare. History and allergen testing are often not reliable in diagnosing the allergic cause of these reactions. Furthermore, literature does not offer consistent evidence that allergen avoidance (aeroallergens and/or food allergens) in children with eczema results in an improvement of established eczema. Therefore, routine allergen testing in children with AD, without a history of immediate-type non-eczematous reactions after allergen exposure, is not necessary, as it has no consequences for disease management.

International guidelines, such as the PRACTALL consensus report, form the EAACI and the AAAI [74], and the ETFAD/EADV position paper [75] describe allergen test procedures, but do not clearly state in which children with eczema, allergy testing should be performed. This decision is left to the clinician, who is often under pressure of the parents to diagnose the allergens that 'cause' the skin disease of their child. The following cases illustrate daily practice dilemmas of allergy testing in children with eczema.

- A child with eczema has no dietary exclusions with a reliable history concerning immediate-type non-eczematous reactions to food allergen exposure. If the history is negative, no food allergen testing is necessary; in case of a positive history, allergen testing can be performed to support the allergic diathesis of the symptoms.
- A child with eczema follows a diet based on former test results showing sensitization to food allergens. If the history shows that the child has used the eliminated foods in the past without a history of immediate-type non-eczematous reactions, reintroduction is recommended supported by a dietician. If the child has not yet been exposed to the eliminated foods or if the history is unreliable, allergen testing should be repeated. Positive test results should be followed by oral challenges if test results are positive.
- The most difficult case is the very young child with severe eczema who has only been exposed to infant formula or breastfeeding. As children with severe eczema have an increased chance to become sensitized to food allergens, allergy testing is frequently performed. However, if food allergen tests are performed, positive test results should be followed by an oral food challenge to avoid unnecessary food eliminations.

Another reason to perform allergy diagnosis is that in some case reports, children exhibit a severe (near) fatal reaction after the first introduction of e.g. peanut, probably due to sensitization to traces of peanut. Although there is some indirect evidence that children with severe eczema are more at risk for developing food allergy, there are no hard data to support that they develop more severe reactions to food than children with milder forms of eczema.

In conclusion, a diagnostic work-up in children with AD without a history of immediate-type non-eczematous reactions after allergen exposure is not necessary. In very young children with eczema, not yet exposed to foods, routinely allergen testing is not necessary. If in individual cases, the decision is made to perform food allergen tests, oral challenges should performed to confirm the diagnoses of food allergy.

Figure 2 summarizes the proposed diagnostic work-up in children with eczema. A careful history, clinical examination and adequate documentation of disease

severity are essential in all children with eczema, irrespective of their disease severity. Allergen testing is not recommended in children with eczema without a history of immediate-type non-eczematous reactions after allergen exposure. If the history is unreliable, allergen testing can be considered, but must be followed by oral food challenges.

Limitations

This article cannot be regarded as a systematic review; however, data from systemic reviews were included when available.

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